Sarcomas of the Gastrointestinal Tract

Separation Into Favorable and Unfavorable Prognostic Groups by Mitotic Count

MATTHEW J. DOUGHERTY, M.D., CAROLYN COMPTON, M.D., MICHAEL TALBERT, M.D., and WILLIAM C. WOOD, M.D.

The authors reviewed the Massachusetts General Hospital experience with primary malignant stromal tumors of the gastrointestinal tract since 1962. Fifty-one of fifty-five lesions were leiomyosarcomas, and the most common anatomic location was the stomach (47%), followed by small intestine (24%), rectum (11%), colon (7%), duodenum (5%), and esophagus (5%). Most patients presented with gastrointestinal bleeding. There were peaks in age incidence in the fourth and sixth decades. All patients underwent surgery initially, and 40 of 55 had resections with "curative intent." Radiation therapy and chemotherapy were employed to a lesser extent, mainly in a palliative setting. The authors found that using number of mitoses per high-power field as the sole determinant of tumor grade yielded two very distinct clinical populations. Patients curatively resected with low-grade lesions had a better than 80% disease-free survival at 8 years, compared with a mean disease-free interval of only 18 months for high-grade lesions. In resectable disease, tumor grade appears to be the single most important prognostic factor. For gastric lesions there was no apparent advantage in extended resections compared with lesser resections encompassing all gross disease. Because of limited numbers of patients, no benefit could be demonstrated for adjuvant radiotherapy.

MALIGNANT STROMAL TUMORS of the alimentary tract are an uncommon entity. The first sizable series was reported by Golden and Stout in 1949,[1] and since then there have been dozens of case reports[2-7] and several large series[8-19] detailing experience with smooth muscle tumors at various sites in the digestive tract. Nonetheless no one institution has had a large enough experience to critically evaluate current therapy, particularly multimodal therapy. This is a review of the Massachusetts General Hospital experience with 55 patients with malignant stromal tumors of the digestive tract treated since 1962, with a review of the literature and discussion of approaches to these lethal tumors.

Address reprint requests to William C. Wood, M.D., Emory University School of Medicine, 1364 Clifton Rd., N.E., Atlanta, GA 30322.

Accepted for publication November 27, 1990.

From the Surgical Oncology Unit and Department of Pathology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts

Methods

Hospital charts of 55 patients who presented between 1962 and 1986 with primary soft tissue sarcomas arising from the esophagus, stomach, duodenum, small bowel, colon, and rectum were reviewed. This included 51 leiomyosarcomas or leiomyoblastomas, two fibrosarcomas, one malignant Schwannoma, and one neurofibrosarcoma. Retroperitoneal sarcomas were not included. Pathology slides of all but four patients were independently and blindly reviewed by two pathologists and graded as "high" if more than 10 mitoses were present per 50 high-power fields, and "low" if there were fewer than this. Tumor size, based on actual measurement of the gross specimen in most cases, and on the surgeon's description in the remainder, also was tabulated. Clinical parameters reviewed included mode of presentation, surgery performed, tumor location, presence of regional or distant metastases at initial operation, whether surgery performed was with "curative intent," and time and location of recurrence, as well as therapeutic modalities employed for primary and recurrent disease.

Of patients reviewed, three were lost to follow-up at less than 5 years (at 0.23 and 36 months). Of the remaining 18 patients alive at last follow-up, the median time followed was 62 months, with a range of 4 to 249 months. Life table survival and disease-free survival were calculated for various subgroups of patients.

Results

There were 31 male and 24 female patients in our series. Ages ranged from 36 weeks' gestation to 87 years of age, with bimodal peaks in the fifth and seventh decades (Fig.

1). Gastrointestinal bleeding was the most common presenting symptom (Fig. 2). Anatomic locations of tumors are illustrated (Fig. 3).

All patients were initially treated surgically. Forty patients (73%) underwent resections that were intended to produce a cure, in other words, all known tumor was encompassed with acceptable gross surgical margins. The remaining 15 patients (27%) were considered incurable because of hepatic or peritoneal sarcomatosis, but all but two had some resection or debulking.

Thirty-two patients died within the period reviewed, all but three from progression of the sarcoma. Patients with initially unresectable disease were treated with some form of palliative surgery in all but two cases. Five of fifteen additionally received radiation or chemotherapy.

Patients with local and distant recurrence were treated with varying combinations of surgery, radiation, and chemotherapy. One patient recurred with a solitary liver metastasis and underwent hepatectomy, but died of operative complications. Of 40 patients who underwent curative resections, 20 (50%) recurred. Seven of these twenty (35%) recurred locally without evidence of distant disease. All seven underwent another resection or attempted resection, five received radiation (one other had received prior adjuvant radiation), and two also received chemotherapy for local recurrence. Six of seven patients died at a mean of 9 months after local recurrence; the other patient was lost to follow-up with known disease 19 months after local recurrence.

Tumors were graded as high or low based solely on the number of mitoses per 50 high-power fields; high grades had 10 or more mitoses per 50 high-power fields, whereas low grades had fewer than 10. Multiple areas of each slide were evaluated, and the highest number of mitoses was used for grading. This yielded 30 high-grade lesions and 22 low-grade lesions. One patient's slides were unavailable for review but was graded as high based on the reported mitotic count on the pathology report. Disease-free survival was plotted for high and low grades for the group subjected to curative surgery (Fig. 4), and life-table survival was plotted for high and low grade lesions in the noncurative resection group (Fig. 5).

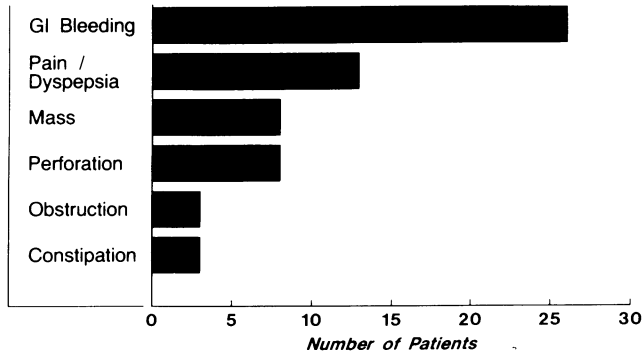

FIG. 2. Symptoms present in patients with malignant stromal tumors of the gastrointestinal tract.

Seven patients received adjuvant radiation for primary disease, in other words, radiotherapy was added although all gross tumor had been removed. Two of these patients received intraoperative radiation. Because the irradiated patients were selected on the basis of clinical assessment of high risk, no comparative analysis can be made.

Median disease-free survival for patients with curative resections with high-grade tumors was 18 months, whereas patients with low-grade tumors curatively resected had a 10-year disease-free survival in excess of 80%. Life-table survival curves were calculated for the group as a whole and for specific primary tumor locations (Fig. 6).

Lastly disease-free survival was plotted for patients who underwent curative resections looking at all grades, large *versus* small tumors (Fig. 7). A large tumor was defined as 5 cm or greater in average diameter, as used in the TNM (tumor, nodes, and metastases) classification system for soft tissue sarcomas.[20]

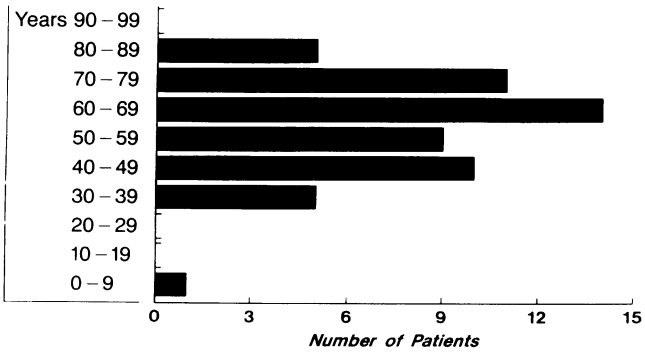

FIG. 1. Distribution of age incidence at presentation with malignant stromal tumors of the gastrointestinal tract.

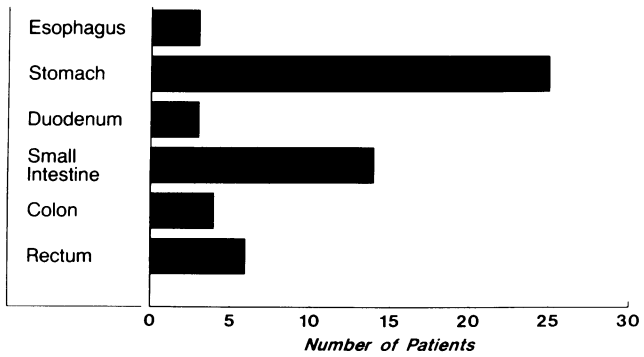

FIG. 3. Location within the gastrointestinal tract of primary malignant stromal tumors.

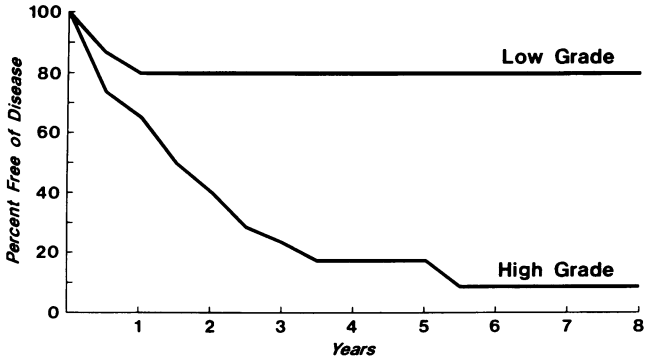

FIG. 4. Disease-free survival in patients resected for cure plotted on the basis of the number of mitoses per 50 high-power fields. High-grade tumors had 10 or more mitoses.

Discussion

Of anatomic sites of the digestive tract, the stomach is the most common location of primary malignant stromal tumors, 38% to 65% of all gastrointestinal leiomyosarcomas in most series,[10,11,13] 47% in our series. This represents approximately 0.25% of all primary stomach malignancies.[14] Although somewhat less common in the small intestine (24% in our series), leiomyosarcomas represent the second most common small bowel malignancy, with an incidence one-third to one-half that of adenocarcinoma.[17,21] Rectal primaries constitute about 7% of these lesions in the literature[1,10,11] (11% of our total), and colonic, duodenal, and esophageal lesions are quite rare in most series, 7%, 5%, and 5% in our series, respectively.

Approximately 50% of patients presented with acute or subacute gastrointestinal bleeding as the major symptom leading to diagnosis. Less commonly pain and dyspepsia, asymptomatic abdominal mass, or perforation of a viscus were the presenting symptoms. Constipation was the predominant symptom in the majority of rectal tumors.

Diagnostic studies employed were highly variable, relating to the mode of presentation, the tumor location, and the year of presentation. Barium contrast studies were employed in most patients. In the 1970s and 1980s, most patients with stomach tumors underwent preoperative endoscopy, although only rarely did it provide a tissue diagnosis. In most patients the diagnosis of malignant stromal tumor was not made preoperatively.

Surgery was the primary treatment for both primary tumors and local recurrences. The surgery employed was highly variable, because of differences in location of tumors, size, involvement of adjacent organs, and preference of the surgeon. Only for stomach lesions were there sufficient numbers of patients undergoing resection for cure to evaluate different surgical approaches. In this group four patients underwent wedge resection of the tumor, four underwent partial gastrectomy, two underwent subtotal gastrectomy, and eight underwent resection of involved adjacent organs, including pancreas, spleen, transverse colon, and esophagus, in addition to gastric resection. Within limits of available follow-up, none of four patients with edge resections recurred, three of four with partial gastrectomies recurred, one of two with subtotal gastrectomy, and four of eight with extended resections. Although there was a slightly higher proportion of high-grade lesions in patients undergoing larger resections, and although there is bias introduced by the surgeon's choice of procedures, one can infer that when feasible, limited resection (*i.e.*, wedge resection for stomach lesions) is adequate. There is nothing to suggest improved recurrence figures for more extensive resections in our experience.

Life-table survivals for the group as a whole *versus* various anatomic locations are depicted in Figure 6. It appears that the prognosis for stomach lesions was a bit better than for small bowel lesions, with 5-year survivals of 35% and 17%, respectively. Survival statistics in the literature range from 40% at 2 years[13] to 57% at 5 years[19] for stomach lesions.[14,16] A 60% 2-year survival has been reported for small bowel lesions,[13] whereas 50% has been reported for 5-year survival for large and small bowel combined.[9] The outcome for duodenal lesions in our series was uniformly poor, but for this and colon, rectum, and esophagus, numbers are too small to give meaningful 5-year survival statistics.

With regard to pathology, we have included four tumors that, based on various pathologic criteria, have been classified as malignant stromal tumors not of leiomyosarcoma histology. We have included these because it is thought that these lesions share the same stem cell origin as the more common leiomyosarcoma, and behave similarly.[22] Much has been written about the importance of histologic grade to prognosis. Russell, Suit, and others have empha-

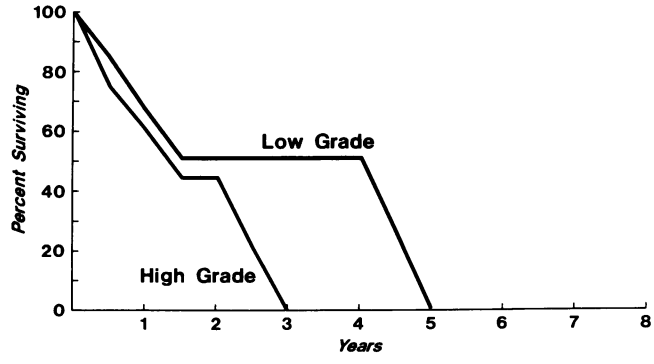

FIG. 5. Overall survival by life-table analysis for patients not resected for cure plotted by grade. High-grade tumors had 10 or more mitoses per 50 high-power fields.

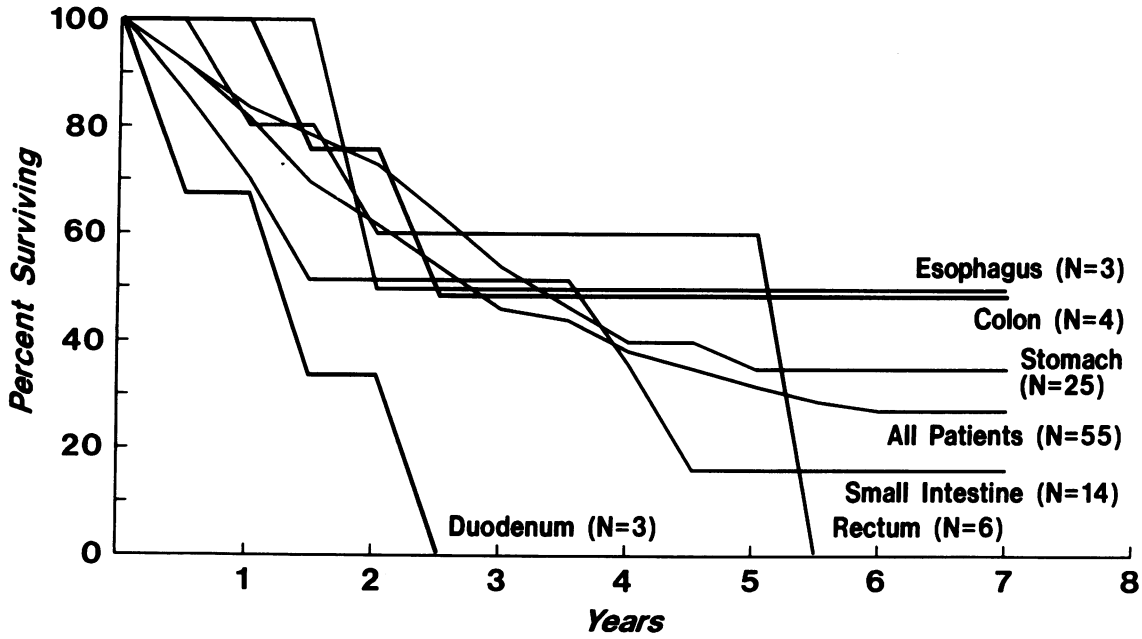

FIG. 6. Life-table survival plotted according to the primary site of the tumor in the gastrointestinal tract.

sized the presence of three clinically distinct tumor grades for soft tissue sarcomas elsewhere,[20] but there is no agreement in the pathology literature as to how many grades of gastrointestinal sarcomas should be recognized, and what criteria define the different grades. We used the number of mitoses per high-power field, which has been recognized as the most important indicator in grading,[13] as the sole determinant of grade. As advocated by Appelman,[22] we used 10 mitoses per 50 high-power fields as the minimum determinant for high-grade lesions, and assigned low grades to the remainder, regardless of other histologic features. This yielded 31 high-grade lesions and 22 low-grade lesions in the group as a whole. Using these criteria for grading resulted in "upgrading" of a significant proportion of patients compared with the original pathologic interpretation, and it is retrospectively apparent that his revised grading was more consistent with the clinical course of most patients. Furthermore there appears to have been a high incidence of undercounting of mitotic activity by those pathologists who originally recorded mitotic counts, leading to further undergrading.

There were roughly equal numbers of high- and low-grade lesions in patients who initially presented with unresectable disease. Although total numbers are small, there appears to be a slightly longer survival in patients with low-grade tumors (Fig. 5). Looking at grade alone in patients curatively resected, there is a significant difference in disease-free survival between the two groups, as has been recognized by others.[9,11-13] The median disease-free survival for all high-grade lesions curatively resected was just over 18 months, whereas low-grade disease-free survival was over 80% at 10 years. Pathologic grade is probably the single most important prognostic factor in patients with resectable disease at presentation.

The classification of leiomyoblastomas, like pathologic grade, is also controversial. Three stomach lesions in our series were called leiomyoblastomas. It is apparent from the literature that these tumors behave like leiomyosarcomas, and the histologic features important to grade are the same.[8,11,12] Although all three leiomyoblastomas in our series were disease free at last follow-up, all three were low-grade lesions.

As low-grade lesions behave quite differently than high-grade lesions, intraoperative determination of grade by

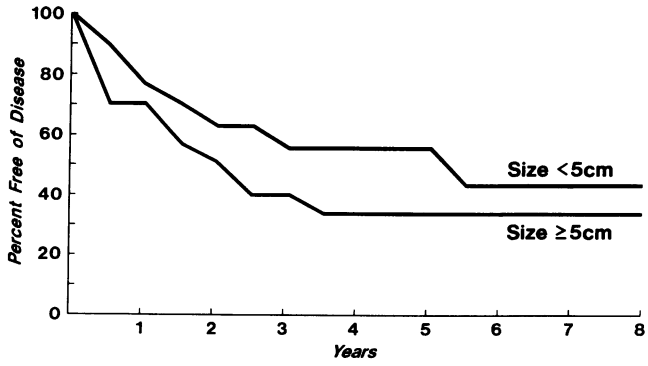

FIG. 7. Influence of tumor size on disease-free survival among patients undergoing curative resection.

frozen section might be helpful in theory.[2] It is our experience, however, and most authors agree, that frozen section grading is quite unreliable.

Tumor size was not reliable either in predicting tumor grade or prognosis. Using 5 cm or greater to define the diameter of large lesions (as is used in the TNM staging system for soft tissue sarcomas),[20] 10 of 18 small tumors were low grade, whereas 22 of 33 large tumors were high grade. Looking at tumor size independent of grade for curatively resected patients, only a small difference in disease-free survival is apparent between large and small tumors (Fig. 7). Thus in contradistinction to sarcomas (including leiomyosarsomas),[23] outside the digestive tract, size did not appear to be an important prognostic indicator in our series, although other authors have suggested that tumor size is important.[7]

The usual mode of failure was intra-abdominal metastasis. In patients with distant recurrent disease, 15 of 19 (79%) had hepatic spread. Eight of nineteen (42%) had studding of serosal and peritoneal surfaces or other intraperitoneal tumor nodules. Only two patients initially recurred distantly outside the abdomen (pulmonary and brain metastases). One of these two had neurofibrosarcoma histology. In patients who were resected palliatively initially, all were considered unresectable because of peritoneal studding or hepatic metastasis. Thus there is no need for extensive preoperative evaluation outside the abdomen to determine resectability when the pathologic diagnosis is known, nor can we advocate such tests to screen for failure after resection. Lymph node metastases were pathologically demonstrated only two patients (4%) in our entire series. This underlies the distinct features of gastrointestinal leiomyosarcomas compared with the more common adenocarcinomas, and argues against extensive lymph node dissections if tumor is known to be a leiomyosarcoma.

Late recurrence has been reported to be common with gastrointestinal leiomyoblastomas,[9] although within the limits of available follow-up this was not true in our series. Only 5 of 20 patients (25%) recurred later than 2 years after initial resection, and the latest recurrence was 42 months, well below our median follow-up time. The median time from resection to recurrence was 14 months. Treatment for recurrence is illustrated in Figure 4, and consisted of varying combinations of surgery, external beam irradiation, and chemotherapy (usually including adriamycin), although in many patients no treatment was employed. Median survival from presentation with distant disease was 7 months.

Of patients initially presenting with unresectable disease, one patient received radiation alone, one radiation and chemotherapy, four chemotherapy alone, and eight no specific therapy beyond initial surgery. Median survival in this group was 12 months, with three patients living 26, 33, and 50 months, respectively.

Seven patients suffered local recurrence without evidence of distant disease. Despite the multiple modalities used in treatment of isolated local recurrence, no patient is disease free.

Six died at a median of 11 months after recurrence, and the other was lost to follow-up with disease 19 months after recurrence. Thus there were no cures in patients with local recurrence. It is impossible to know how many patients suffered local failure that was not recognized until distant disease was present.

Radiation therapy has been used chiefly in a palliative setting in this and other series. Seven patients received adjuvant radiation, two of them intraoperatively. We could not demonstrate a difference in disease-free survival in this group compared with patients not receiving adjuvant radiation. Of note six of seven patients so treated had high-grade lesions. Once again the small number of patients receiving adjuvant radiotherapy, the variable dosages, and patient selection factors in this retrospective analysis do not allow conclusions to be drawn from these data. Experience with soft tissue sarcomas in other anatomic locations, however, suggests a significant role in adjuvant and possibly primary treatment with radiation. Tepper and co-workers[24] have treated retroperitoneal sarcomas that have been resected, partially resected, or not resected and found improved survival and local control with radiotherapy, particularly with dosages greater than 6400 cGy.[24] Likewise primary radiation controlled soft tissue sarcomas of various anatomic sites, again with best control at dosages greater than 6400 cGy, in another series.[25] Suit and others[26–28] have shown good results in soft tissue sarcomas of various histology occurring in the extremities, combining radical radiotherapy with limited surgical resection. Sorbe[29] showed that local failure could be diminished in uterine leiomyosarcoma when radiation was added, although only if gross disease was left behind and was not in a true adjuvant setting.

It may be that the "radioresistance" of leiomyosarcomas often cited by other authors[3,14,16] is a function of inadequate dosage. To attain a dosage of more than 6000 cGy within the abdomen to treat either gross or microscopic residual disease, the intraoperative technique is most promising. Only two patients in our series received intraoperative radiation in adjuvant setting, both of whom had high-grade lesions (one duodenal, one gastric), with survivals of 29 and 41 months, respectively. One other patient was treated for pelvic recurrence of a rectal primary with intraoperative radiation alone and was lost to follow-up with residual disease 19 months later.

Given the significant incidence of isolated local failure (35% of all recurrences), and its uniformly poor outcome,

a case can be made for attempting to improve local control with radiation therapy, including boost doses delivered intraoperatively, at least in high-grade lesions. Ideally this should be studied in a prospective randomized fashion, but the rarity of these tumors does not allow such a trial.

The problem of microscopic metastatic disease at the time of presentation has yet to be dealt with effectively. Results with adjuvant chemotherapy for uterine leiomyosarcoma have been disappointing.[30,31] Dacarbazine and adriamycin are the most significant additions to the armamentarium,[32,33] and response rates from 15% to 45% have been demonstrated with palliative treatment.[32-36] No patients in our series received adjuvant chemotherapy for primary disease, and we are unable to draw conclusions regarding palliative chemotherapy.

Summary

We have presented the Massachusetts General Hospital experience with malignant stromal tumors of the gastrointestinal tract, most of which were leiomyosarcomas. Anatomic incidence, presentation, patient demographics, and survival statistics were described and are consistent with reports from other institutions. We found that using mitotic activity alone to determine tumor grade delineated two remarkably different clinical populations, and found tumor grade to be the most important prognostic indicator for patients with resectable disease.

A significant proportion of patients suffered isolated local failure. Distant failure almost invariably consisted of hepatic and intra-abdominal sarcomatosis, and only rarely were lymph node metastases or isolated extra-abdominal metastases seen. Because of the retrospective nature of this study and small numbers, no benefit could be demonstrated for adjuvant radiotherapy. Patients receiving chemotherapy lived longer than patients who did not in the unresectable group, although patient selection factors make the difference uninterpretable.

References

1. Golden T, Stout AP. Smooth muscle tumors of the gastrointestinal tract and retroperitoneal tissues. Surg Gynecol Obstet 1941; 73: 784–810.
2. Crocker DW. Smooth muscle tumors of the stomach. Ann Surg 1969; 170:239–243.
3. Dodds JJ, Beahrs OH. Leiomyosarcoma of the duodenum. Am J Surg; 1963; 105:245–249.
4. Sagi A, Feuchtwanger M, Yanai I, Walfisch S. Smooth muscle tumors of the small bowel: a case report and review of the literature. J Surg Oncol 1985; 30:120–123.
5. Schumann F. Leiomyosarcoma of the colon: report of a case and review of treatment and prognosis. Dis Colon Rectum 1972; 15: 211–216.
6. Somervell JL, Mayer PF. Leiomyosarcoma of the rectum. Br J Surg 1971; 58:144–146.
7. Taylor PH. Leiomyosarcoma of the stomach. Br J Surg 1969; 56: 187–192.
8. Abramson DJ. Leiomyoblastomas of the stomach. Surg Gynecol Obstet 1973; 1336:118–125.
9. Akwari OE, Dozois RR, Weiland LH, Beahrs OH. Leiomyosarcoma of the small and large bowel. Cancer 1978; 42:1375–1384.
10. Anderson PA, Dockerty MB, Buie LA. Myomatous tumors of the rectum (leiomyomas and myosarcomas). Surgery 1950; 48:642–650.
11. Evans HL. Smooth muscle tumors of the gastrointestinal tract. Cancer 1985; 58:2242–2250.
12. Morrissey K et al. Muscular tumors of the stomach: clinical and pathological study of 113 cases. Ann Surg 1973; 178:148–155.
13. Ranchod M, Kempson RL. Smooth muscle tumors of the gastrointestinal tract and retroperitoneum. Cancer 1977; 39:255–262.
14. Remine WH. Gastric sarcomas. Am J Surg 1970; 120:320–323.
15. Salmella H. Smooth muscle tumors of the stomach. Acta Chir Scand 1968; 134:384–391.
16. Shiu MH et al. Myosarcomas of the stomach. Cancer 1982; 49:177–187.
17. Starr GF, Dockerty MB. Leiomyomas and leiomyosarcomas of the small intestine. Cancer 1955; 8:101–111.
18. Stout AP. Bizarre smooth muscle tumors of the stomach. Cancer 1962; 15:400–409.
19. Welch JP. Smooth muscle tumors of the stomach. Am J Surg 1975; 130:279–285.
20. Russell WO et al. A clinical and pathological staging system for soft tissue sarcomas. Cancer 1977; 40:1562–1570.
21. Dodds WJ et al. Leiomyosarcoma of the small intestine. Am J Roentgenol 1969; 107:142–149.
22. Appelman H. Smooth muscle tumors of the gastrointestinal tract. Am J Surg Pathol 1986; 10(1):83–99.
23. Wile AG, Evans HL, Romsdahl MM. Leiomyosarcoma of soft tissue: a clinicopathologic study. Cancer 1981; 48:1022–1032.
24. Tepper JE et al. Radiation therapy of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 1984; 10:825–830.
25. Tepper JE, Suit HD. Radiation therapy alone for sarcoma of soft tissue. Cancer 1985; 56:475–479.
26. Suit HD et al. Preoperative radiation therapy for sarcoma of soft tissue. Cancer 1981; 47:2269–2274.
27. Suit HD et al. Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. Cancer 1985; 55:2659–2667.
28. Suit HD, Russel WO. Radiation therapy of soft tissue sarcomas. Cancer 1975; 36:759–764.
29. Sorbe B. Radiotherapy and/or chemotherapy as adjuvant treatment of uterine sarcomas. Gynecol Oncol 1985; 20:281–289.
30. Hannigan EV, Freedman RS, Rutledge FN. Adjuvant chemotherapy in early uterine sarcoma. Gynecol Oncol 1983; 14:56–64.
31. Omura GA et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a gynecologic oncology group study. J Clin Oncol 1985; 3:1250–1245.
32. Gottlieb JA et al. Role of DTIC in the chemotherapy of sarcomas. Cancer Treat Rep 1976; 60:199–203.
33. Wilbur JR et al. Chemotherapy of sarcomas. Cancer 1975; 36:765–769.
34. Bedikian AY et al. Chemotherapy for sarcoma of the stomach. Cancer Treat Rep 1970; 63:411–414.
35. Benjamin AY et al. Advances in the chemotherapy of sarcomas. Med Clin North Am 1977; 61:1039–1043.
36. Subramanian S, Wiltshaw E. Chemotherapy of sarcoma. Lancet 1978; 1:683–686.